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Ventilator-Associated Pneumonia Prevention Methods Using Topical Antibiotics

Herd Protection or Herd Peril?

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Ventilator-associated pneumonia (VAP) develops in approximately 20% of patients in the ICU receiving prolonged mechanical ventilation (MV). Among the range of methods for preventing VAP, the evidence base for topical antibiotics (TAs), including selective digestive decontamination, appears to be the most compelling. However, several observations are puzzling, and the contextual influence resulting from concurrent use of both topical placebo and TA within an ICU remains untested. As with herd protection conferred by vaccination, contextual influences resulting from a population-based intervention cannot be estimated at the level of a single trial. Estimating contextual effects requires multilevel random-effects methods. In this way the dispersion in VAP incidence across groups from 206 studies, as cited in various-source systematic reviews, was calibrated. The benchmark mean VAP incidence derived from 49 observational groups of patients receiving MV is 23.7% (95% CI, 20.6%-27.2%). In contrast, for 20 and 15 concurrent control groups from the TA evidence base that did vs did not receive topical placebo, respectively, this incidence is 38% (95% CI, 29%-48%) and 33% (95% CI, 20%-50%). This contextual influence remains significant in a meta-regression model adjusted for group-level variables, such as within a trauma ICU context. The mean VAP incidence for five other categories of control groups from the broader evidence base is within four percentage points of the benchmark. The contextual effect of TA is paradoxic, peculiar, potent, perfidious, and potentially perilous. The TA evidence base requires reappraisal to consider this herd peril.

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ABBREVIATIONS: CRCDBT = concurrent randomized controlled double-blind trial; MV = mechanical ventilation; SDD = selective digestive decontamination; TA = topical antibiotic; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) develops in approximately 20% of patients in the ICU receiving prolonged mechanical ventilation (MV).[1-8] Moreover, the estimated attributable mortality rate of VAP is 13%.[9] Bacterial colonization originating partially from either the GI or the upper respiratory tracts and partially from cross-colonization

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within the ICU precedes the development of VAP (Fig 1). Hence, there are multiple potential sites at which this progression from colonization through to VAP might be disturbed.

A wide range of VAP prevention methods have been studied. Sixteen systematic reviews[10-25] contain abstracted VAP incidence data for 157 groups across a broad evidence base of VAP prevention methods. In addition, three systematic reviews contain abstracted VAP incidence data for 49 groups from observational studies.[4-6]

The methods of VAP prevention can be broadly classified into nonantibiotic-based methods delivered through either the gastric route,[10-14] the airway route,[15-20] or the oral care route[21-23] and various antibiotic-based methods.[23-26] The gastric route methods include various types of stress ulcer prophylaxis (two systematic reviews,[10,11] 17 studies), enteral feeding (one systematic review,[12] eight studies), and probiotics (two systematic reviews,[13,14] 10 studies). The various airway route methods include secretion drainage (two systematic reviews,[15,16] 24 studies), inspired air humidification (one systematic review, 12 studies),[17] secretion management by body posturing (two systematic reviews,[18,19] 16 studies), and programmed circuit changes (one systematic review,[20] two studies). The oral care methods (three systematic reviews,[21-23] 16 studies) studied were of various antiseptics, such as chlorhexidene and tooth brushing.

On the other hand, antibiotic-based methods, such as selective digestive decontamination (SDD), are based on the administration of antibiotics to the oropharynx topically through a nasogastric tube to the stomach and possibly parenterally. These studies are summarized in three systematic reviews (40 studies)[23-25] and a meta-analysis[26] and can be further classified into those in which control groups were concurrent with the study group and received no placebo, concurrent and received placebo alone, concurrent and received up to 5 days of parenteral antibiotics routinely (duplex studies), and nonconcurrent.

The evidence base for topical antibiotics (TAs) appears the most compelling. In meta-analyses of studies of TAs

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both with concurrent[23-26] and with nonconcurrent[26] control groups, the apparent reduction in VAP incidence is $>50\%$, whereas in studies of methods of VAP prevention other than TAs the reduction is $<50\%$.[10-20]

The challenges to study design in the evaluation of these various VAP prevention methods are several.[26-28] First, there are presumably unknown risk factors for VAP in addition to the known risk factors, such as admission for trauma.[27-29] Second, multiple definitions for VAP are available, and which is the most objective and unambiguous is debatable.[30] Some studies have avoided VAP as a study end point altogether.[31]

These two challenges are optimally controlled within a concurrent randomized controlled double-blind trial (CRCDBT) study design. First, the randomized assignment of patients to concurrent control and intervention groups minimizes bias arising from confounding in that all risk factors for the study end point, whether known or unknown, are distributed randomly between the groups. Second, concealing group allocation through the use of a matching placebo minimizes observer bias resulting from diagnostic ambiguity. Third, in defining the evidence base and in deriving summary estimates, studies with these attributes are graded with a higher quality of study design and are preferentially included over unblinded studies and studies that use historic control groups.

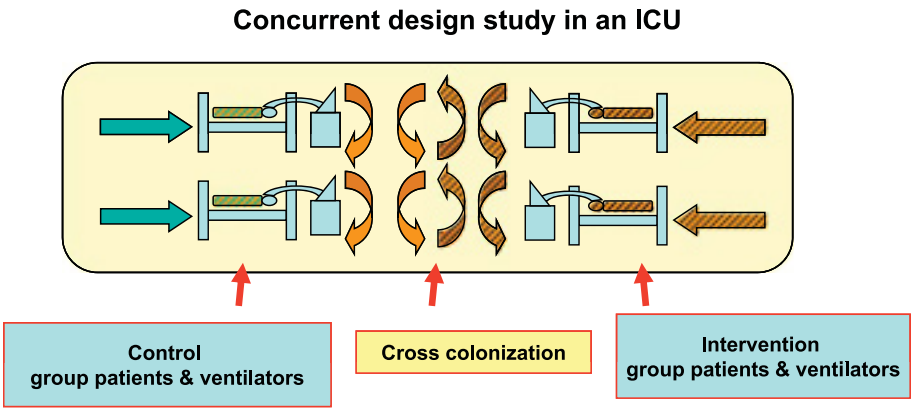

Figure 1 – *Schematic of control and intervention patients receiving mechanical ventilation in an ICU. Color coding within horizontal arrows represent different colonizing flora, and circular arrows represent contextual effects resulting from cross-colonization.*